Health Canada Santé Canada

Guidance Document

Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document

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Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

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Ligne directrice: Changements survenus après l'avis de conformité (AC) : Document sur l'innocuité et l'efficacité.

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Document change log

Date: June 13, 2015 (posted August 26, 2015)

Nature of and/or reason for change:
Changes were made to the document to reflect amendments to the Food and Drug Regulations: Regulations Amending the Food and Drug Regulations (Labelling, Packaging and Brand Names of Drugs for Human Use) which came into force on June 13, 2015 for prescription products and those administered or obtained through a health professional.

Date: February 2, 2016 (posted February 8, 2016)

Nature of and/or reason for change:
Changes made to reflect Level II and Level III changes no longer require the submission of mock-ups under the Plain Language Labelling requir[illegible]ts.

Date: February 19, 2018 (posted June 26, 2018)

Nature of and/or reason for change:
Changes are mainly administrative (e.g., rewording sections to add clarity to existing text, addition/deletion of examples, the addition of new terms to the glossary and clarification of when Level III changes should be filed and the documentation that should be submitted).

Consequential changes were to reflect the requirements of new initiatives that have been implemented over the past several years such as: the interim measure on how Health Canada initiated safety changes for human drugs under Vanessa's Law (2014) are managed; the Plain Language Labelling (PLL) requirements for all non-prescription drugs that came into force on June 13, 2017, with the additional requirement of the Canadian Drug Facts Table on the outer label, and as part of the PLL initiative, certain sections of the Guidance Document: Product Monograph were revised that resulted in changes to this guidance, (e.g., Part III: Consumer Information changed to Part III: Patient Medication Information and the removal of the References section).

Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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1. Introduction

1.1 Objectives

(a) To assist with the classification of safety and efficacy changes made to a new drug that has received a Notice of Compliance (NOC) pursuant to paragraph C.08.004 (1) (a) of the Food and Drug Regulations.

(b) To provide sponsors with recommendations on what would be considered sufficient data to support a proposed label change and to allow a determination of the impact of the change on the safety, efficacy or effective use of a new drug.

1.2 Scope and application

This guidance document applies to sponsors intending to make changes to new drugs that have received a NOC pursuant to section C.08.004 of the Food and Drug Regulations. These new drugs may include pharmaceuticals, biologics, and radiopharmaceuticals for human use and pharmaceutical and certain biotechnological products for veterinary use[1], including those submissions for which a NOC has been recommended but issuance of the NOC has been placed on hold.

This guidance document should be read in conjunction with other related Health Canada documents as well as the following associated post Notice of Compliance (NOC) changes documents:

- the Post-Notice of Compliance (NOC) Changes: Framework for further background information, reporting categories, and a list of policies and guidance documents that were superseded,
- the Post-Notice of Compliance (NOC) Changes: Quality, and
- the Notice: How Health Canada is managing safety updates when a serious health risk is identified under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law) (April 22, 2016)

Information regarding general submission requirements and target performance standards may be found in the Health Canada guidance documents: the Management of Drug Submissions (for human drugs) or the Management of Regulatory Submissions (for veterinary drugs).

2. Guidance for implementation

Reporting Categories

The following criteria and examples are meant to provide guidance with respect to the classification of a safety or efficacy related change. For assistance in classifying a change, sponsors are advised to contact Health Canada. Contact information is provided in the Guidance Document: Management of Drug Submissions (for human drugs) or the Guidance for Industry: Management of Regulatory Submissions (for veterinary drugs).

2.1 Level I - Supplements

2.1.1 Criteria

A Level I change is defined as a change to the label of a drug that has the potential to increase the exposure levels of the drug, either by expanding the population that is exposed (i.e. related to market expansion), or by increasing individual exposure. Label changes that can result in increased exposure levels of the drug include:

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1 The Veterinary Drugs Directorate (VDD) should be consulted to determine if the submission constitutes a veterinary biotechnological drug under the Food and Drugs Act.

(a) The addition or expansion of a safety claim or efficacy claim, whether explicit or implied.
(b) The addition of a new route of administration, new dosage form, new strength, or change in duration of treatment or changes in recommended dose/dosing range.
(c) The deletion or reduction of existing risk management measures.
(d) This level also includes changes that do not meet the above criteria but require the filing of a Level 1 - Supplement[2]:
(e) The brand name of the new drug has been changed.[3]
(f) An existing indication has been withdrawn in its entirety or the indication has been modified for the purpose of risk/harm management including a reduction in scope.
(g) An existing route of administration, dosage form and/or strength has been removed following the cancellation of the DIN(s).
(h) The results of confirmatory clinical trials (either intermediate or final) specified in the Letter of Undertaking.[4]
(i) A submission for the purpose of obtaining Data Protection Extension[5].
(j) Significant changes exclusive to label design elements for drugs for human use.
(k) Health Canada initiated label changes of pharmaceuticals, biologics, and radiopharmaceuticals products for human use that are "necessary to prevent injury to human health" under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law). Refer to the Notice: How Health Canada is managing safety updates when a serious health risk is identified under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law) (April 22, 2016).

k) For non-prescription drug products, any deviation from the standard Canadian Drug Facts Table (CDFT)[6,7]

2.1.2 Examples

Examples of Level I changes include but are not limited to the following:

- Health Canada initiated label changes that may include but are not limited to: the addition of a new contraindication, a change in an existing contraindication, the addition of a serious warning or precaution (for human drugs), the addition of a human warning to a veterinary drug, or the tightening of clinical monitoring requiring a change to the labels of sections of the Product Monograph/Package Insert.
- Changes to the existing text of the label that refers to any potential benefits of the drug (implied or explicit), including claims regarding the safety profile or efficacy. This includes changes in text with reference to sub-populations for human drugs; and for veterinary drugs, the different age groups (puppies versus dogs) or production types (dairy versus beef cattle), and any reference to possible claims regarding side effects.
- Addition of a new indication, reintroduction of an indication that received a Notice of Compliance and was subsequently withdrawn, or the revision to existing text of a current indication.
- Addition of a new species for a veterinary drug.
- Addition of a new route of administration, dosage form, or strength.

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2 As required in Sections C.08.003 and C.08.004.1 of the Food and Drug Regulations.

3 Only if there is a change in the product name but the same Drug Identification Number (DIN) is retained. For all other changes in manufacturer's name and/or product name, refer to the " "Guidance Document Administrative Processing of Submissions and Applications: Human or Disinfectant Drugs (2017)", the "Guidance for Industry: Review of Drug Brand Names (2014)", the "Guidance Document Questions and Answers: Plain Language Labelling Regulations (2015)" or the "Guidance Document: Questions and Answers: Plain Language Labelling Requirements for Non-prescription Drugs (2017)".

4 Refer to the "Notice of Compliance with Conditions Policy" (2016).

5 Refer to the "Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations".

6 Refer to the "Good Label and Package Practices Guide for Non-Prescription Drugs and Natural Health Products".

7 Refer to the "Guidance Document: Drugs Facts Table for Non-Prescription Drugs".

- A change regarding the mechanism of action of the drug as detailed in the Action and Clinical Pharmacology (Clinical Pharmacology for veterinary drugs) sections of the Product Monograph/Package Insert[8] that results in an explicit or implicit claim.
- A change to the Clinical Trial (Safety and Efficacy Study Information for veterinary drugs) sections of the Product Monograph/Package Insert which results in a new claim, explicit or implied (e.g., listing of additional outcome measures, or revision to the description of study design such that a new benefit is implied for a specific sub-population).
- Data has been added from an efficacy or safety (tolerability) study in a special population.
- A change in condition of use from prescription to non-prescription status.
- An existing contraindication, warning or cautionary text anywhere in the Product Monograph/Package Insert, has been deleted in its entirety, has been modified to reflect a reduction or diminishment in risk/harm, and/or in a risk management measure. For veterinary drugs, this also includes a reduction to an existing withdrawal/withholding period. These may result from a range of supporting data (e.g., post-marketing data, safety studies, pharmacokinetic data etc.).
- Existing text regarding an adverse event or set of events has been modified to reflect, in any way, an apparent reduction in risk/harm. This includes changes related only to animal data (for human drugs), or non-target species data (for veterinary drugs).
- The existing text of the label (e.g., Package Insert or Part I or Part III[9] of the Product Monograph) have been deleted, reworded and/or otherwise modified to diminish a risk/harm management measure. This would include any change in the conditions of use as a result of new pharmacokinetic data related to a special or sub-population or new species (for veterinary drugs).

For drug products for (human use), changes exclusive to labelling design elements which include:

- Adding new graphics or symbols (other than symbols required by regulations) or changing locations of graphics that will impact readability of key elements of the inner or outer label (e.g. addition of a symbol that relates to the type of packaging being used).
- Changing the size or colour of text or background in connection with product name (proprietary and non-proprietary), warnings, dosage, expression of strength, route of administration, population, and storage (particularly for vaccines).
- Reordering text on the label necessary for the safe and effective use of the product:

  i) Moving label information to different panels.

  ii) Changing the order of information presented on the principal display panel including product name (proprietary and non-proprietary), warnings, dosage, expression of strength, route of administration, population, and storage (particularly for vaccines).

- Reducing overall label size.
- Changing the package design, where the package is the immediate container.
- Increasing the size of company logo/graphics.

For non-prescription drug products (for human use), in addition to the above changes in design elements:

- Use of graduated flexibilities or innovative labels.

This list is not exhaustive; it is meant to provide guidance on the types of changes that require the filing of a submission for review. Health Canada encourages sponsors to contact the appropriate Directorate should they require further direction on the most appropriate submission type and/or class to file. Information regarding Plain Language Labelling can be found in the Guidance Document Questions and Answers: Plain

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8 For veterinary drugs, the package insert is the equivalent to the Product Monograph for human drugs.

9 Referred to as the Patient Medication Information in the "Guidance Document: Product Monograph".

Language Labelling Regulations or the Guidance Document: Questions and Answers: Plain Language Labelling Regulations for Non-prescription Drugs and Contact Lens Disinfectants.

2.1.3 Submission filing

Changes included in this reporting category, along with the recommended supporting data (refer to section 4), shall be filed, with Health Canada as a Supplement to a New Drug Submission (SNDS), a Supplement to an Extraordinary Use New Drug Submission (EU SNDS), a Supplement to an Abbreviated New Drug Submission (SANDS), or a Supplement to an Extraordinary Use Abbreviated New Drug Submission (EU SANDS).

For drug products, changes exclusive to labelling design elements should be filed as a SNDS/SANDS Labelling only or an EU-SNDS/EU-SANDS Labelling only[10].

2.2 Level II (90 day) Notifiable Changes

2.2.1 Criteria

A Level II (90 day) Notifiable Change (i.e. risk/harm management change) is defined as a change to the label that has the potential to improve the management of risk/harm to the population currently indicated for use of the drug, or in any other way exposed to the drug by:

(a) The identification or characterization of any adverse events (i.e., any risk or harm).
(b) The addition or strengthening of risk management measures, including instructions on dosing or any other conditions of use.
(c) The identification of subgroups, or conditions of use, for which the benefit/risk profile of the new drug has the potential to be less favourable.

Note: Some changes that meet the Level II (90 day) NC criteria may require the filing of a Level I - Supplement.

2.2.2 Examples

Examples of Level II (90 day) changes include but are not limited to the following:

- An addition to, strengthening or clarification of text anywhere in these sections: Contraindications, Warnings and Precautions (Cautions for veterinary drugs) and Adverse Events. These changes may include the provision of recommended risk/harm management actions (e.g., required testing prior to initiation of the drug, specific monitoring during product use, ensuring patient awareness of certain risks, etc.), or the identification of a specific sub-population as being at greater risk such as those with a concomitant condition, those taking concomitant medicine, or a specific age group.
- The instructions for use including dosage and administration, in the Product Monograph (Part I or Part III) or the Package Insert have been reworded and/or otherwise altered with respect to risk/harm management to optimize the safe use of the drug.
- A new drug interaction or pharmacokinetic study has been added, or an existing drug interaction has been better characterized that identifies a risk/harm.
- A change to the toxicology data, explicitly or implied, stating an increase in risk/harm to the target population (other changes to the toxicology data, in general, are filed as Level II (120 day) NCs.
- A change to improve the clarity of the message to patients/clients, in Part III of the Product Monograph (for human drugs) or the Client Information section of the Package Insert (for veterinary drugs).
- Revisions to the existing text of the labels to add clarity to the safe use of the drug, but without expanding, explicitly or implied, the claims of the drug.

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10 Labelling material that does not include supporting clinical, non-clinical data or chemistry and manufacturing data.

Note: Label changes for human drugs that affect the labelling design elements are to be filed as Level I - Supplements.

2.2.3 Submission filing

Changes included in this reporting category should be filed, along with the recommended supporting data (refer to section 4), to Health Canada as a Level II (90 day) Notifiable Change.

2.3 Level II (120 day) Notifiable Changes (NCs)

2.3.1 Criteria

A Level II (120 day) change is defined as any change to the label that does not meet the criteria of a Level I change, a Level II (90 day) NC or a Level III change, but for which prior approval by Health Canada is required.

This new category was developed to differentiate among Level II changes so that the more urgent Level II (90 day) NCs (i.e., those that involve risk/harm management) can be given priority in the processing and review queue.

2.3.2 Examples

Examples of Level II (120 day) changes include but are not limited to the following:

- Changes to the text related to the Overdose section (e.g., additional overdose symptoms or treatments).
- Changes made to the text of the Pharmacology, Microbiology, Toxicology sections of the Product Monograph/Package Insert, except where criteria for Level II (90 day) NCs are met.
- A new drug interaction or pharmacokinetic study has been added, or has been better characterized with no risk/harm identified and does not expand the claim of the drug, explicitly or implied.
- The addition of data or modification of text, other than Level II (90 day) or Level III changes, which does not result in any other changes to the information provided to the Health Care Professional or patient/consumer and for which the sponsor is not seeking a statement that may be interpreted as a new claim.
- The existing text of the Product Monograph for human drugs has been converted from the "old" to the "new" format. Refer to the Guidance Document: Product Monograph (2016/12/09).

This list is not exhaustive; it is meant to provide guidance on the types of changes which would be considered acceptable as the different Level II changes. Health Canada encourages sponsors to contact the appropriate Directorate should they require further direction.

2.3.3 Submission filing

The changes included in this reporting category should be filed, along with the recommended supporting data (refer to section 4), to Health Canada as a Level II (120 day) change.

2.4 Level III Changes - Annual Notifications

2.4.1 Criteria

A Level III change is defined as any change to the label that is not expected to impact the safety, efficacy, and/or effective use of the drug. The changes included in this reporting category may be implemented by the sponsor without prior review by Health Canada of the data supporting such a change.

2.4.2 Examples

Examples of Level III related changes include but are not limited to the following:

- The existing text of the labels (for human drugs) have been revised to add clarity and maintain consistency with common label phrase standards (e.g., change from "Product Monograph available on request" to "Product Monograph available to health care professional on request", change from "Not recommended for children" to "Not for use in children" or "Keep out of reach of chil

- Revisions to Part III, Patient Medication Information section of the Product Monograph (for human drugs) to standardize text in each of the following sections: Overdose, Missed Dose, How to Store It or Reporting Suspected Side Effects.
- Any change in spelling of the text of the label (e.g., "adition" is replaced by "addition").

For drug products (for human use), examples of Level III changes include but are not limited to the following non-significant label changes:

- Updating bar codes and technical codes,
- Removing graphics,
- Removing non-regulatory label information,
- Changing colour of graphics where there is no text overlay or changing colour of company logo,
- Correcting spelling errors, and
- Updating contact information (e.g., customer service number, website addresses, etc.)

For non-prescription drug (for human use), any change to the layout of the label that does not represent a change to the requirements of Sections C.01.004 and A.01.017 of the Food and Drug Regulations (e.g. contrast, artwork, font, and/or position) or the terms of market authorization.

For non-prescription drugs for human use; changing from the old label format to the standard Canadian Drug Facts Table (CDFT).

For veterinary drugs, any change to the layout of the label that does not represent a change to the requirements of Sections C.01.004 and A.01.017 of the Food and Drug Regulations (e.g., contrast, artwork, font, and position) or the terms of market authorization.

This list is not exhaustive; it is meant to provide guidance on the types of changes which would be considered acceptable as Level III changes. Health Canada encourages sponsors to contact the appropriate Directorate should they require further direction.

2.4.3 Submission filing

Notification of a Level III label change should be filed at the time the change is implemented using the Post-Notice of Compliance (NOC) Changes: Notice of Change - Level III Form.

A copy of the revised annotated labels, Product Monograph/Package Insert should only be submitted with the filing of the next Level I - Supplement or Level II NC that necessitates a label change as well. The dates of implementation for these Level III changes should be clearly identified.

Level III changes do not require the submission of mock-up labels[11] under the Plain Language Labelling requirements.

Supporting data for Level III changes recommended in this guidance document should not be submitted; however, the data should be available to Health Canada within thirty (30) calendar days of a request.

3. Pre-Submission Enquiries

Prior to filing a submission, sponsors are advised to contact Health Canada if:

i) any of the conditions (a-e) listed below apply to the proposed change;

(a) For Level 1 changes, only one clinical trial/study[12] is available or the data package is comprised solely of publications[13].

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11 Veterinary drugs are excluded from the Plain Language Labelling requirements.

12 Not applicable to drugs for veterinary use.

13 Refer to the "Guidance Document: Drug Submissions Relying on Third-Party Data (

(b) The clinical trial/study makes use of an end point or statistical method that is new or not validated.

(c) The clinical trial/study does not reach statistical significance for the primary endpoint or the endpoint used to support the change.

(d) The clinical trial/study made use of a comparator authorized but not available on the Canadian market.

(e) For Subsequent Entry Products where:

- the Canadian Reference Product (CRP) is no longer marketed[14].
- the approval of a strength outside of the CRP dosing range is sought.
- the clinical trial/study or publication makes use of a non-Canadian reference product as a comparator[15].

ii) the existing guidances/policies are unclear or do not cover specific situations, or

iii) if the sponsor wishes to discuss product specific data requirements.

Depending on the issue or concern, a pre-submission meeting may be arranged to allow more in-depth discussion between the sponsor and Health Canada. Contact information and procedures are provided in Health Canada's Guidance Document: Management of Drug Submissions for drugs intended for human use, and the Guidance for Industry: Management of Regulatory Submissions for drugs intended for veterinary use.

4. Documentation

Health Canada has the mandated responsibility to perform a thorough and rigorous assessment on a drug submission received for a change to a new drug and render an evidence and context-based decision within a specified time frame.

The intent of this section is to highlight the range in categories of data and contextual information that may be relevant to the evaluation of a particular submission.

Regulatory decision-making is optimal when conducted in the context of additional information submitted which could include the following:

- characterization of the patient or treated population in question,
- regional clinical practice standards,
- the availability of alternative therapies,
- the sponsor's interpretation of the data,
- the interpretation by other major international agencies (e.g., as per labels approved by that jurisdiction), and
- information that no other major agency has rendered an opinion at the time of the evaluation or if discussions are currently underway.

The presence of an information category in these lists does not necessarily mean the data is required. However, it is anticipated that when a specific topic is relevant to a submission, the sponsor will acknowledge and address it by either providing the information, or a rationale as to the absence of the information. This will help to minimize delays that can result when a submission is silent on a relevant topic. As stated in the

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Experience)".

14 Refer to the "Guidance Document: Use of a Foreign-sourced Reference Product as a Canadian Reference Product".

15 Refer to the "Guidance Document: Use of a Foreign-sourced Reference Product as a Canadian Refer... Product".

Foreword of this document, alternate approaches to the principles and practices described in this document may be acceptable to Health Canada provided they are supported by adequate justification.

The associated Guidance Document: Post-Notice of Compliance (NOC) Changes: Framework should be consulted for details regarding the filing of submissions and Level III changes -Annual Notifications to Health Canada. Documentation recommended in Section 2.2.3.3 of the aforementioned guidance should be included with a Level I, Level II (90 day) or Level II (120 day) filing and Section 2.2.4 provides details of the documentation to be included with Level III label changes.

The recommended data to support safety and efficacy changes, mentioned below, should be included or commented on, where applicable, in the submission package for Level I, Level II (90 day), and Level II (120 day) changes.

4.1 Filing formats for submitting supporting data - Level I and Level II Changes

Data required to support the change(s) should be provided with the submission in electronic format as prescribed in the "Notice - Mandatory use of the Electronic Common Technical Document (eCTD) format", and the "Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document Format" or the "Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format" depending on the submission type. A Comprehensive Summary: Bioequivalence (CS: BE) should also be completed and provided where applicable. For veterinary drug submissions, data should be prepared and filed as prescribed in the "Guidance for Industry: Preparation of Veterinary New Drug Submissions" and the "Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format".

4.2 Supporting data common to Level I and Level II Changes

The following should be included in a Level I and Level II changes submission package, where applicable:

(a) An annotated and non-annotated electronic copy of the labels (e.g., Product Monograph, prescribing information, patient medication information, package inserts, package labels). Refer to the "Notice: Updates to the Guidance Document Questions and Answers: Plain Language Regulations or the Guidance Document Questions and Answers: Plain Language Labelling Regulations for Non-prescription Drugs and Contact Lens Disinfectants".

Additions to the text should be highlighted, deletions should be indicated by strikeout and references to the specific location of the information within the submission should be provided. Level II changes do not require the submission of mock-ups under the Plain Language Labelling requirements.

4.3 Supporting data

(a) Clinical and/or non-clinical trial/study data relevant to the submission. This may include but is not limited to: clinical trials (whether focused on efficacy or safety), bioequivalence trials, pharmacokinetic studies, pharmacodynamic studies, epidemiological data/study results, pharmacovigilance studies, Periodic Safety Update Report (PSUR) data, review reports/analysis of specific safety concerns, risk management plans/pharmacovigilance plans or patient registry data.
(b) Other data which may be relevant to the submission. This may include, but is not limited to: rationales, real world information regarding drug use, declarations/attestations, opinion papers, conference presentations, publications in peer-reviewed scientific journals and drug utilization information.
(c) All Level I Changes for human drugs requires bilingual mock-up labels accompanied by the Packages Certification Form[16].
(d) Notifiable Changes (NCs) for human drugs do not require mock-ups of the labels. In place of mock-ups,

16 Refer to the "Notice: Updates to the Guidance Document Question and Answers: Plain Language Labelling Regulations" or the "Guidance Document Questions and Answers: Plain Language Labelling Regulations Non-prescription Drugs and Contact Lens Disinfectants".

annotated written text is considered acceptable to reflect any proposed changes. Sponsors are expected to submit this written text in both official languages, as well as the mock-up labels and the Packages Certification Form. If a sponsor submits mock-ups for these types of submissions, the design elements may not be reviewed.

4.4 Contextual information

(a) A submission involving safety and efficacy updates to the Product Monograph should include a copy of the most recent company core data safety sheet[17].
(b) Copies of the most recent labels authorized in other major International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/ International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (ICH/VICH) regulatory jurisdictions (including Food and Drug Administration (FDA), European Union (EU), Therapeutic Goods Administration (TGA), Australian Pesticides Veterinary Medicines Authority (APVMA).
(c) Correspondence or communications from other major ICH /VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA) which may be relevant to the submission or a statement confirming that such communications have not been required by any authorities.
(d) For subsequent entry products, the revision date and control number of the Product Monograph (Package Insert for veterinary drugs) of the Canadian Reference Product used in preparation of the generic sponsor's Product Monograph/Package Insert.
(e) For additional information on filing safety labelling changes for subsequent entry pharmaceutical products, refer to the "Notice - Notification of Safety Labelling Changes to the Product Monographs of Pharmaceutical Drug Products".

4.5 Additional contextual information specific to Level I Changes

(a) The current status, with respect to other major ICH/VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA) (e.g., currently under review, approved, rejected, or not submitted) at the time of submitting the proposed change to Health Canada.
(b) Where the review has been completed by other major ICH/VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA), a summary of any significant issues raised, how they were addressed and resolved or; a statement confirming that there were no significant issues identified by those authorities. Where available, copies of any foreign review reports, correspondence or communications (including Questions and Answers) which may be relevant to the submission.
(c) Where the review has not yet been completed by other major ICH/VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA), a summary of any significant issues being raised.
(d) Where under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law), Health Canada has initiated safety updates to the labels of pharmaceuticals, biologics, and radiopharmaceuticals for human use, new data may not be required; however, a copy of the advisement letter should be included with the submission.

4.6 Additional contextual information specific to Level II (90 day) Changes

(a) Wording of any related instructions or communications (translated into English or French) to Health Care Professionals that may have been or is currently required in other major ICH/VICH regulatory jurisdictions (including FDA, EU, TGA, and APVMA) or a statement confirming that such instructions or communications have not been required by any authorities.
(b) The most recent electronic or hard copy of the Periodic Safety Update Reports (PSURs). These can be cross-referenced if previously provided to Health Canada.
(c) The Company Core Data Safety Sheet[18].

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17 Not applicable to drugs for veterinary use.

18 Not applicable to drugs for veterinary use.

4.7 Supporting data - Level III Changes

Any data that may have been generated by the sponsor in support of a Level III change should not be submitted but is to be available to Health Canada within thirty (30) calendar days of a request.

5. Glossary

Adverse Drug Reaction (ADR)
As defined in the Food and Drug Regulations means a noxious and unintended response to a drug, this occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function.

Adverse Event (AE)
Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug product, whether or not considered related to the drug product.

Canadian Drug Facts Table (CDFT)
A table on the outer label of a non-prescription drug or contact lens disinfectant that displays information required by the Regulations in a standardized, easy-to-read format (table faits de drogue).

Claim
A word, sentence, picture, symbol, graph or paragraph on product labels, package inserts or advertisements where the representation for sale is capable of being understood as the capacity of producing a desired result or effect in terms of efficacy or as being safe or comparatively safer from undergoing or causing undue hurt, injury or loss as safety claims. Therefore, a claim may include any representation or statement that would communicate a "positive" interpretation of the drug product rather than a potential risk/harm.

Claims can be considered as explicit or implied by using the following:

i) Choice of language:

- explicit is when the representation for sale is fully revealed or expressed without vagueness or ambiguity leaving no question as to meaning or intent
- implied is when the representation for sale is capable of being misunderstood or misinterpreted so as to imply or suggest something in addition to what is explicit

ii) Placement within the Product Monograph/Package Insert:

- There are two sections of the PM/PI that are intended for explicit claims: Indications and Clinical Trials. In contrast, the remaining sections of the PM/PI are not expected to include claims, and therefore if present, would typically be considered as implied.

Client:
The owner of an animal that is being treated, an authorized representative of the owner or an individual who the veterinarian reasonably determines is acting in the interest of the animal.

Company Core Safety Sheet
A corporate document maintained by the drug sponsor that contains relevant safety information regarding a drug for human use.

Conditions of Use
Any language used in the labels, Product Monograph/Package Insert that provides instructions or recommendations (explicit or implied) to the prescriber/ patient/client regarding the use of the product.

Label
Label includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package (Food and Drugs Act) (e.g., product monograph, package insert, inner and outer labels etc.).

Mock-Up
A full colour, actual size copy of the labels and a colour representation of the packages intended to be used for the sale of the drug, including all presentation/design elements, proposed graphics, fonts, colours and text (with a place holder for expiry date, Drug Identification Number (DIN0, and lot number).

New Drug
As per section C.08.001 (for the purposes of the Act and Division 8 of the Food and Drug Regulations):

(a) a drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug,
(b) a drug that is a combination or two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug, or
(c) a drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug.

Package
Package includes anything in which any food, drug, cosmetic or device is wholly or partly contained, placed or packed (Food and Drugs Act).

Package Insert (Human Drugs)
Contains the prescribing information required for the safe and appropriate prescribing, dispensing and administering of a prescribed drug product. This is equivalent to Part I, Health Information of the Product Monograph for new drugs. In addition to Part I, the information described in Part III (Patient Medication Information) may also be provided as part of the package insert for a new drug product. Both documents are intended for use by a healthcare professional. Refer to the Product Monograph text below for more information on Parts I and III.

Package Insert (Veterinary Drugs)
The factual, scientific document for a veterinary drug product that, devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug (i.e., equivalent to the Product Monograph for human drugs).

Patient
A patient can be a human, an animal or a group of animals (e.g., herd of cattle).

Patient Medication Information (Human Drugs
The information described in Part III (Patient Medication Information) of the Product Monograph contains information for the patient. This portion of the Product Monograph identifies the information that is to be provided to the patient either at the time of dispensing as a separate document, or as a package leaflet.

Patient Registries (Human Drugs)
A database or list of patients within a particular group (e.g., pregnancy, type of cancer, genetic disease, organ transplant). Its purpose is to provide an organized collection of secondary/post-authorization data.

Pharmacovigilance Studies
Studies involving the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

Prescribing Information (Human Drugs)
The information described in Part I (Health Professional Information) of the Product Monograph contains the prescribing information, and serve the following purposes:

- It identifies the information to be provided if a package insert is included with a new drug product.
- It identifies information to be provided as part of all professional material and that may be used for promotional and advertising purposes, other than in the case of reminder notices.

In addition to Part I, the information described in Part III (Patient Medication Information) may also be provided as part of the package insert for a new drug product.

Product Monograph[19] (Human Drugs)
The factual, scientific document for a human drug product that is devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of a new drug. This information is provided with the drug at point of sale. Each product monograph consists of three distinct parts:

Part I: Health Professional Information
Contains information required for the safe and appropriate prescribing, dispensing and administering of the drug product.

Part II: Scientific Information
Contains more in-depth scientific/research information such as toxicology and data from animal studies and human clinical trials. It complements and extends the information contained in Part I.

Part III: Patient Medication Information
Contains information derived from Parts I and II that helps the patient understand what the medication is, how to use it and what the potential side effects are. It is also intended to serve as a guide for health professionals to easily identify the information needed for counselling patients. It is presented in a language and format that is appropriate for a patient audience, including the general public. Part III is required for all drugs, regardless of the location of use (e.g., hospital) or method of administration (e.g., by a third party).

Withdrawal Period/Withholding Period
The length of time between the last administration of a drug to an animal and the time when tissues or products collected from the treated animal for consumption as food contain a level of residue of the drug would not likely cause injury to human health. (Section C.01.001 (1) of the Food and Drug Regulations).

19 Refer to the "Guidance Document: Product Monograph"